REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following reasons.

I. Status of the Claims

Claims 25-35 and 76-86 were cancelled previously. Claims 91-99 are added with exemplary support in working examples 1, 3 and 4. Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 1-24, 36-75 and 87-99 will be pending.

II. Statement of the Substance of the Examiner's Interview

Applicants thank Examiner Tran for the courtesy extended during an interview with Applicants' representative, Yang Tang, on June 10, 2011. During the interview, possible claim amendments to limit the dosage form to a fast melt or controlled release formulation and to limit the surface stabilizer to hydroxypropyl cellulose were discussed. Pursuant to Examiner Tran's request, Applicants informally submitted the proposed claim amendments for further consideration. However, Applicants have not yet received any response from Examiner Tran regarding the proposed claim amendments. Accordingly, Applicants add new dependent claims 91-98 which limit the dosage form a fast melt formulation or a controlled release formulation and the surface stabilizer to hydroxypropyl cellulose in this response and timely file the response before expiration of the statutory response period.

III. Rejection of Claims under 35 U.S.C. §103(a)

The Examiner advances the following rejections:

(1) Claims 1-15, 17-24, 40-75 and 87-90 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over U.S. Patent No. 5,510,118 to Bosch et al. ("Bosch") in view of PCT Publication No. WO 98/31360 by Stamm et al. ("Stamm");

(2) Claim 16 is rejected under 35 U.S.C. §103(a) for allegedly being obvious over Bosch in view of Stamm, and further in view of GB 2316316 to Baralle et al. ("Baralle"); and

(3) Claims 36-39 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over Bosch in view of Stamm, and further in view of U.S. Patent No. 4,389,397 to Lo et al. ("Lo").

Applicants respectfully traverse each rejection. The tertiary references, Baralle and Lo, are cited for the alleged teachings of a bimodal particle distribution (Office Action, the paragraph bridging pages 4 and 5) and of the viscosity of the liquid dosage form (*id.*, at page 5, last two paragraphs), respectively. Neither of the tertiary references compensates for the deficiencies of the primary and secondary references as detailed below. Because all of the rejections rely on the same primary reference, Bosch, and the same secondary reference, Stamm, Applicants choose to address the rejections collectively in the following paragraphs.

The Examiner asserts that it would have been obvious to select the glipizide active agent of Stamm and formulate the glipizide active agent using Bosch's process because: (i) glipizide is a well known water-insoluble drug; (ii) there is an art-recognized need to improve dissolution and bioavailability of glipizide; and (iii) Bosch's formulation is suitable for improving bioavailability of a wide variety of active agents including anti-diabetic agents.

A. The prior-art teaching of a genus does not render the claimed species obvious.

First, the Examiner's rejection ground is based on the incorrect presumption that all water-insoluble drugs can be successfully formulated into a stable nanoparticulate active agent composition. This presumption does not have any valid basis in the cited reference. In reaching this conclusion, the Examiner appears to overly generalize the teaching of Bosch to encompass any water-insoluble drug. This position is contradictory to MPEP 2144.08 regarding the obviousness of a species when prior art teaches a genus. The MPEP specifically sets forth that the prior-art teaching of a genus does not render the claimed species obvious and requires the

Examiner to consider many factors, such as the size of the genus, the express teachings, the teachings of structural similarity, the teachings of similar properties or uses, the predictability of the technology, etc.

In the present case, the genus of water-insoluble drugs is tremendously broad, covering numerous compounds. The Examiner has failed to meet the initial burden to articulate a rationale as to why the skilled artisan would have selected the species of the claimed invention, glipizide.

B. Unpredictability in the art is established by the accompanying declaration.

Applicants submit herewith a declaration under 37 C.F.R. §1.132 executed by Dr. Gary Liversidge to demonstrate the unpredictability in the art and hence, the lack of a reasonable expectation of success in obtaining a stable nanoparticulate glipizide composition.

(1) Declaration evidence of unpredictability in the formation of nanoparticulate active agents

As submitted in the Liversidge Declaration (¶¶ 27-30), not all active agents can be formulated into stable nanoparticulate active agent compositions. It is important to emphasize that this unpredictability ***remains to the present day.*** For example, ¶ 29 cites to Wu et al., "Physical and chemical stability of drug nanoparticles," *Advanced Drug Delivery Reviews*, electronically published in February, 2011, which reports "that it remains challenging to obtain nanoparticulate active agent compositions that are physically and chemically stable because the stability is affected by many factors. *See* lines 84-105 and 855-861." ¶ 29. Liversidge Declaration at ¶ 30 continues:

> *More specifically, Wu et al. teach that obtaining a stable nanoparticulate active agent composition is hindered by the difficulty of selecting a suitable surface stabilizer for the active agent. Moreover, according to Wu et al. the main challenges in designing nanoparticulate drug formulations are: (i) the lack of a*

> *fundamental understanding of the interaction between the surface stabilizer and the active agent nanoparticles (see lines 268-273); (ii) the process of selecting a surface stabilizer having an appropriate anchoring tail to the particular active agent is burdensome (see lines 268-273); (iii) the lack of predictability due to the lack of any correlation between the physiochemical properties of the active agent and the success rate of obtaining a stable nanoparticulate active agent composition (see lines 399-402); and (iv) the lack of an efficient and high throughput screening technique to identify a suitable surface stabilizer (see lines 812-816).*

Id. Similarly, despite the existence of different technologies to make nanoparticulate active agents, there is no predictability in success with any one technology, or with ***any*** technology, at all. Indeed, each technology has its own drawbacks (Liversidge Declaration at ¶ 27), which adds an additional layer of consideration and unpredictability in formulating any one drug. Dr. Liversidge concludes that "not all active agents can be successfully made into nanoparticulate active agent formulations in view of the technologies available to date." ¶ 28.

For example, as Dr. Liversidge attests, the drug clopidogrel could not be formed into a stable nanoparticulate clopidogrel composition despite numerous attempts with different surface stabilizers and formulation approaches. ¶ 31.

Thus, not only do ***not all combinations of surface stabilizers and an active agent*** form a stable nanoparticulate active agent composition, but ***not all active agents*** can be formulated into a nanoparticulate active agent composition. Dr. Liversidge's declaration therefore corrects the impression that making a stable nanoparticulate active agent composition is merely routine and predictable in view of the art available to date.

(2) Improved bioavailability is not a predictable result of forming a nanoparticulate active agent composition

As demonstrated by the Liversidge Declaration, nanoparticulate active agent compositions ***do not*** always exhibit improved bioavailability or reduced fed-fast variability.

Moreover, the data described in the Liversidge Declaration demonstrate that the only way to determine if formulating an active agent into a nanoparticulate composition will improve bioavailability and/or result in reduced fed/fasted variability is to make a nanoparticulate active agent formulation and then test the formulation to see if an improvement in bioavailability or a reduction in fed/fasted variability is obtained; the results cannot be predicted but rather must be drawn from actual working data.

The data described herein are relevant to the obviousness rejection made by the Examiner in the present case because there is no guarantee that obtaining a nanoparticulate active agent composition will achieve the desired results of improved bioavailability and related properties. These data are also relevant to the obviousness rejection because it demonstrates that the unpredictability extends not only to the making of nanoparticulate drugs, but also to the properties of nanoparticulate drugs, and hence their use in therapeutic contexts. The assumption of *prima facie* predictability in the making and using a nanoparticulate drug is contradicted by the data and Dr. Liversidge's declaration.

a. Nanoparticulate Compound A and nanoparticulate ketoprofen does not exhibit improved bioavailability as compared to microparticulate Compound A and microparticulate ketoprofen

Specifically, as explained in Dr. Liversidge's declaration, ¶ 4:

> *U.S. Patent No. 7,217,431 ("the '431 patent") demonstrates that a nanoparticulate formulation of a drug substance according to Elan's nanotechnology does not improve in vivo bioavailability of the drug in comparison to other non-nanoparticulate formulations of the same drug substance. See Example 4, which is summarized in the following paragraphs. This data therefore demonstrates that a researcher cannot predict whether an active agent will exhibit an improved pharmacokinetic profile by reformulating the active agent into a nanoparticulate formulation.*

Similarly, a "nanoparticulate ketoprofen composition and the microparticulate ketoprofen composition demonstrated similar performance in bioavailability (represented by C_{max} and AUC)." Liversidge's declaration at ¶ 4, referring to Vergote et al., "*In vivo* evaluation of matrix pellets containing nanocrystalline ketoprofen," *Int'l. J. Pharm.*, *240*: 79-84 (2002).

b. It is not possible to predict whether a drug formulated into a nanoparticulate drug formulation will exhibit maximum bioavailability in the presence or in the absence of food

Evidence that nanoparticulate drug formulations do not always eliminate the food effect of the drug in comparison to non-nanoparticulate formulations of the same drug is provided in Liversidge's declaration at ¶¶ 12-26, reporting data from: Nexavar® (sorafenib tosylate, ¶¶ 12-16); megestrol acetate (¶¶ 17-20); cilostazol (¶¶ 21-23); and MK-0869 (¶¶ 24-25). Dr. Liversidge concludes at ¶ 26 that "it is not possible to predict whether a drug formulated into a nanoparticulate drug formulation will exhibit maximum bioavailability in the presence or in the absence of food."

(3) The assertion of predictability relies on hindsight bias

Further, the assumption of predictability appears to derive from a common and pervasive error in logic. In particular, the Examiner appears to consider that Applicants' success in making nanoparticulate glipizide is merely a routine application of prior-art technology represented by Bosch, and practiced on numerous diverse drugs. This conclusion is made by the Examiner on the basis of Applicants' own success.

The conclusion is, however, based on an incomplete data set because Applicants ***cannot*** file patent applications on ***failures***. A failed experiment does not even meet the most basic requirement of utility under 35 U.S.C. § 101. There is also little incentive to publish negative results, leading to one of the major causes of "publication bias." *See e.g.,* Wikipedia entry on "publication bias" (attached herewith as Exhibit 1).

In private industry, often the only evidence of scientific activity is the generation of a successful product because private industry exists not for publishing scientific data but for producing such products. Moreover, such data may be subject to various contractual obligations from other parties. Thus, for example, if the patent owner of drug A contracts with a company to make and test a particular formulation, such as a nanoparticulate formulation, the owner of drug A typically reserves all rights to publication of the data. Therefore, unless there is a ***successful*** drug formulation leading to a product, such data will often not be released.

The only area of research in which there is widespread publication of negative data is human clinical trials, and this is true only because the leading medical journals adopted a specific policy, and because of the vital important public interest in identifying adverse effects. *See e.g.*, Editorial "Clinical Trial Registration – Looking Back and Moving Ahead", *N. Engl. J. Med.*, 356(26):2734-2736 (June 28, 2007), submitted herewith as Exhibit 2.

Thus, the assumption of predictability arises from a selective and non-representative data set and is merely an aspect of hindsight bias against which one must strive to avoid. *See e.g., In re McLaughlin,* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

(4) Unpredictability established on the record supports the lack of a reasonable expectation of success.

In view of the much greater unpredictability, Applicants remind the Examiner of the USPTO's 2010 *KSR* Guidelines, citing to *In re Omeprazole Patent Litigation*, 536 F.3d 1361 (Fed. Cir. 2008), noting that "one situation when it is important to identify a ***reason*** to combine known elements in a known manner to obtain predictable results is when the combination requires a greater expenditure of time, effort, or resources than the prior art teachings" (emphasis added). The art of pharmaceutical formulation is time consuming and expensive, and requires a high level of skill. Accordingly, obviousness in this context requires more than a mere suggestion to try, it requires that the result of a combination of glipizide and a surface stabilizer

can reasonably be ***predicted*** in advance. This has not been demonstrated, and is rebutted by the evidence at hand.

Moreover, the reason or suggestion to adopt the technology of Bosch to make a nanoparticulate glipizide composition presumes that a stable nanoparticulate glipizide composition could be obtained, and that such a nanoparticulate glipizide composition would exhibit superior bioavailability (or "potency"). *See* final Office Action, the paragraph bridging pages 5 and 6. However, as shown in Dr. Liversidge's Declaration, it is not predictable that a nanoparticulate form of any given drug could be made and would have improved bioavailability, or other improved properties, such as a reduced food effect. There is, therefore, no *prima facie* reason or suggestion that the recited composition would be superior for the treatment of diabetes, and therefore no reason or suggestion to undertake the time and expense to make this (per *Omeprazole*).

(5) Claims 91-98 benefit from additional grounds of patentability.

Claims 91-98 recite surface stabilizers suitable for a nanoparticulate glipizide composition and a specific dosage form (fast melt or controlled release) of the nanoparticulate glipizide composition as demonstrated in the working examples. The Examiner has yet to explain why the skilled artisan would have selected the particularly claimed surface stabilizers and obtained the specific dosage form in light of the teachings of the cited references.

In conclusion, the asserted rejections rely on a combination of references that does not render the claims obvious because: (a) there is no real world reason or suggestion to combine the references; (b) the combination of references does not result in the claimed composition with a reasonable expectation of success in view of the evidence of unpredictability; and (c) the requirement for predictability is particularly high in the context of time consuming, expensive, pharmaceutical arts.

In view of the foregoing, the Examiner has not met his burden of establishing a sufficient *prima facie* case of obviousness. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: August 10, 2011

By _____

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EXHIBIT 1

Publication bias

From Wikipedia, the free encyclopedia

Publication bias is the tendency of researchers, editors, and pharmaceutical companies to handle the reporting of experimental results that are *positive* (i.e. showing a significant finding) differently from results that are *negative* (i.e. supporting the null hypothesis) or inconclusive, leading to bias in the overall published literature. Such bias occurs despite the fact that studies with significant results do not appear to be superior to studies with a null result with respect to quality of design.[1] It has been found that statistically significant results are three times more likely to be published than papers affirming a null result.[2] It also has been found that the most common reason for non publication is the failure of an investigator to submit (on account of loss of interest, null results etc.), underlining researchers' role in publication bias phenomena.[1]

In an effort to decrease this problem some prominent medical journals require registration of a trial before it commences so that unfavorable results are not withheld from publication. Several such registries exist, but researchers are often unaware of them. In addition, attempts to identify unpublished studies have proved very difficult and often unsatisfactory. Another strategy suggested by a meta-analysis is caution in the use of small and non-randomised clinical trials because of their demonstrated high susceptibility to error and bias.[1]

Contents

Definition

> “ Publication bias occurs when the publication of research results depends on their nature and direction.[3] ”

Positive results bias, a type of publication bias, occurs when authors are more likely to submit, or editors accept, positive than null (negative or inconclusive) results.[4] A related term, "the file drawer problem", refers to the tendency for negative or inconclusive results to remain unpublished by their authors.[5]

Outcome reporting bias occurs when several outcomes within a trial are measured but these are reported selectively depending on the strength and direction of those results. A related term that has been coined is HARKing (**H**ypothesizing **A**fter the **R**esults are **K**nown).[6]

The file drawer effect

The file drawer effect, or file drawer problem, is that many studies in a given area of research may be conducted but never reported, and those that are not reported may on average report different results from those that are reported. An extreme scenario is that a given null hypothesis of interest is in fact true, i.e. the association being studied does not exist, but the 5% of studies that by chance show a statistically significant result are published, while the remaining 95% where the null hypothesis was not rejected languish in researchers' file drawers. Even a small number of studies lost "in the file drawer" can result in a significant bias.[7]

The term was coined by the psychologist Robert Rosenthal in 1979.[8]

Effect on meta-analysis

The effect of this is that published studies may not be truly representative of all valid studies undertaken, and this bias may distort meta-analyses and systematic reviews of large numbers of studies—on which evidence-based medicine, for example, increasingly relies. The problem may be particularly significant when the research is sponsored by entities that may have a financial interest in achieving favorable results.

Those undertaking meta-analyses and systematic reviews need to take account of publication bias in the methods they use for identifying the studies to include in the review. Among other techniques to minimize the effects of publication bias, they may need to perform a thorough search for unpublished studies, and to use such analytical tools as a Begg's funnel plot or Egger's plot to quantify the potential presence of publication bias. Tests for publications bias rely on the underlying theory that small studies with small sample size (and large variance) would be more prone to publication bias, while large-scale studies would be less likely to escape public knowledge and more likely to be published regardless of significance of findings. Thus, when overall estimates are plotted against the variance (sample size), a symmetrical funnel is usually formed in the absence of publication bias, while a skewed asymmetrical funnel is observed in presence of potential publication bias.

Extending the funnel plot, the "Trim and Fill" method has also been suggested as a method to infer the existence of unpublished hidden studies, as determined from a funnel plot, and subsequently correct the meta-analysis by imputing the presence of missing studies to yield an unbiased pooled estimate.

Examples of publication bias

One study[9] compared Chinese and non-Chinese studies of gene-disease associations and found that "Chinese studies in general reported a stronger gene-disease association and more frequently a statistically significant result".[10] One possible interpretation of this result is selective publication (publication bias).

Risks and remedies

Risks

According to John Ioannidis, negative papers are most likely to be suppressed:[11]

1. when the studies conducted in a field are smaller
2. when effect sizes are smaller
3. when there is a greater number and lesser preselection of tested relationships
4. where there is greater flexibility in designs, definitions, outcomes, and analytical modes
5. when there is greater financial and other interest and prejudice
6. when more teams are involved in a scientific field in chase of statistical significance.

Ioannidis further asserts that "claimed research findings may often be simply accurate measures of the prevailing bias".

Remedies

Ioannidis' remedies include:

1. Better powered studies
   - Low-bias meta-analysis
   - Large studies where they can be expected to give very definitive results or test major, general concepts
2. Enhanced research standards including
   - Pre-registration of protocols (as for randomized trials)
   - Registration or networking of data collections within fields (as in fields where researchers are expected to generate hypotheses after collecting data)
   - Adopting from randomized controlled trials the prineiples of developing and adhering to a protocol.
3. Considering, before running an experiment, what they believe the chances are that they are testing a true or non-true relationship.
   - Properly assessing the false positive report probability based on the statistical power of the test[12]
   - Reconfirming (whenever ethically acceptable) established findings of "classic" studies, using large studies designed with minimal bias

Study registration

In September 2004, editors of several prominent medical journals (including the *New England Journal of Medicine*, *The Lancet*, *Annals of Internal Medicine*, and *JAMA*) announced that they would no longer publish results of drug research sponsored by pharmaceutical companies unless that research was registered in a public database from the start.[13] Furthermore, some journals, e.g. *Trials*, encourage publication of study protocols in their journals.[14]

See also

- Adversarial collaboration
- Confirmation bias
- Counternull
- Funding bias
- Meta-analysis
- Null hypothesis
- Parapsychology
- Peer review
- Reporting bias
- Selection bias

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External links

- The Truth Wears Off: Is there something wrong with the scientific method? -- Jonah Lehrer (http://www.newyorker.com/reporting/2010/12/13/101213fa_fact_lehrer)
- Skeptic's Dictionary: positive outcome bias (http://skepdic.com/posoutbias.html).
- Skeptic's Dictionary: file-drawer effect (http://skepdic.com/filedrawer.html).
- Journal of Negative Results in Biomedicine (http://www.jnrbm.com/)
- The All Results Journals (http://www.arjournals.com/)
- Journal of Articles in Support of the Null Hypothesis (http://www.jasnh.com/)
- interesting article on 'the decline effect' and the role of publication bias in that (http://www.newyorker.com/reporting/2010/12/13/101213fa_fact_lehrer?currentPage=all).

EXHIBIT 2

EDITORIAL

Clinical Trial Registration — Looking Back and Moving Ahead

Christine Laine, M.D., M.P.H., Richard Horton, F.Med.Sci., Catherine D. DeAngelis, M.D., M.P.H., Jeffrey M. Drazen, M.D., Frank A. Frizelle, M.B., Ch.B., M.Med.Sc., Fiona Godlee, M.B., B.Ch., B.Sc., Charlotte Haug, M.D., Ph.D., M.Sc., Paul C. Hébert, M.D., M.H.Sc., Sheldon Kotzin, M.L.S., Ana Marusic, M.D., Ph.D., Reuben Saloj, M.S., Ph.D., Torben V. Schroeder, M.D., D.M.Sc., Harold E. Sox, M.D., Diana B. Van Der Weyden, M.D., and Frank W.A. Verheugt, M.D.

N Engl J Med 2007; 356:2734-2736, June 28, 2007

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In 2005, the International Committee of Medical Journal Editors (ICMJE) initiated a policy requiring investigators to deposit information about trial design into an accepted clinical trials registry before the onset of patient enrollment.[1] This policy aimed to ensure that information about the existence and design of clinically directive trials was publicly available, an ideal that leaders in evidence-based medicine have advocated for decades.[2] The policy precipitated much angst among research investigators and sponsors, who feared that registration would be burdensome and would stifle competition. Yet the response to this policy has been overwhelming. The ICMJE promised to reevaluate the policy in 2 years after implementation. Here, we summarize that reevaluation, specifically commenting on registries that meet the policy requirements, the types of studies that require registration, and the registration of trial results. As is always the case, the ICMJE establishes policy only for the 12 member journals (a detailed description of the ICMJE and its purpose is available at www.icmje.org), but many other journals have adopted our initial trial registration recommendations, and we hope that they will also adopt the modifications discussed in this update (see Table).

Key Summary Points

The research community has embraced trial registration. Before the ICMJE policy, ClinicalTrials.gov, the largest trial registry at the time, contained 13,153 trials; this number climbed to 22,714 1 month after the policy went into effect.[3] In April 2007, the registry contained over 40,000 trials, with more than 200 new trial registrations occurring weekly (Zarin D, personal communication). The four other registries that meet the ICMJE criteria have also grown as scores of journals have adopted the ICMJE clinical trials registration policy. In response to burgeoning registration, many investigators, sponsors, and government agencies have asked the ICMJE to recognize their local registries as databases that meet the policy. Fortunately, the World Health Organization's (WHO) International Clinical Trial Registry Platform (ICTRP), which was nascent when the ICMJE began to require trial registration, has matured rapidly and provides options for those that desire a wider array of registries. The ICTRP has taken the first steps toward developing a network of primary and partner registers that meet WHO-specified criteria.[4] Primary registers are WHO-selected registers managed by not for profit entities that will accept registrations for any interventional trials, delete duplicate entries from their own register, and provide data directly to the WHO. Partner registers, which will be more numerous, will include registers that submit data to primary registers but limit their own register to trials in a restricted area (such as a specific disease company, academic institution, or geographic region).

The ICMJE strongly supports the WHO's efforts, through the ICTRP, to develop a coordinated process for identifying, gathering, deduplicating, and searching trials from registries around the world, thus eventually providing a one-stop search portal for those seeking information about clinical trials. In addition to the five existing registries, the ICMJE will now also accept registration in any of the primary registers that participate in the WHO ICTRP. Because it is critical that trial registries are independent of for profit interests, the ICMJE policy requires registration in a WHO primary register (rather than solely in a partner register, since for profit entities manage some partner registers). As

previously. Trial registration with missing or uninformative fields for the minimum data elements is inadequate.

Initially, the ICMJE restricted registration of all clinically directive trials, which it defined as "any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome."[1] In May 2005, the ICMJE revised this definition to exclude preliminary trials designed to study pharmacokinetics or major unknown toxicity (phase 1 trials).[2] However, the ICMJE recognizes the potential benefit of having information about preliminary trials in the public domain, because these studies can guide future research or signal safety concerns. Consequently, the ICMJE is expanding the definition of the types of trials that must be registered to include these preliminary trials and adopts the WHO's definition of clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."[3] Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. As previously, purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) will not require registration. The ICMJE member journals will start to implement the expanded definition of clinically directive trials for all trials that begin enrollment on or after July 1, 2005. Those who are uncertain whether their trial meets the expanded ICMJE definition should err on the side of registration if they wish to seek publication in an ICMJE journal.

Over the time during which registration of trial methods has become common practice, several forces have begun advocating for registration of trial results. We recognize that the climate for results registration will probably change dramatically and unpredictably over coming years. For the present the ICMJE will not consider results posted in the same primary clinical trials register in which the initial registration resides as previous publication if the results are presented in the form of a brief (≤500 words) structured abstract or table. The ICMJE favors a standard abstract format for results reporting, and the CONSORT (Consolidation Standards for the Reporting of Trials) group's forthcoming guidelines for abstracts related to trials may be one such option. The ICMJE believes that parties interested in results registration should consider retaining the deposition of such an abstract in the registry 24 months after closure of data collection if results are not published in a peer-reviewed venue by that time. The registered abstract should either cite any related full, peer-reviewed publications or include a statement that indicates that the report has not yet been published in a peer-reviewed journal. Researchers should be aware that editors may consider more detailed deposition of trial results in publicly available registries to be prior publication. When submitting a paper, authors should fully disclose to editors all posting in registries of results of the same or closely related work.

Three years ago, trials registration was the exception; now it is the rule. Registration facilitates the dissemination of information among clinicians, researchers, and patients, and it helps to assure that participants that the information that accrues as a result of their altruism will become part of the public record. The WHO's global efforts toward comprehensive trials registration and the ICMJE's requirements for registration are to increase public trust in medical science.

Potential financial conflicts of interest: *Employment*: Dr. Godlee was previously editorial director of *Current Controlled Trials*, which owns the ISRCTN (International Standard Randomised Controlled Trial Number) trials register; Mr. Kotzin is employed by the National Library of Medicine, which produces ClinicalTrials.gov; Mr. Kotzin is not responsible for activities or policies regarding ClinicalTrials.gov. *Expert testimony*: F. Godlee. *Other*: R. Horton (co-chair, WHO ICTRP Scientific Advisory Group); J.M. Drazen (member, WHO ICTRP Scientific Advisory Group); H.C. Sox (member, WHO ICTRP Scientific Advisory Group); M.B. Van Der Weyden (member, government advisory committee for the Australian and New Zealand Clinical Trials Registry).

This article (10.1056/NEJMe078110) was published at www.nejm.org on June 4, 2007.